

## Corneal Cross-linking

**Policy** MP-024

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### Disclaimer:

1. Policies are subject to change in accordance with State and Federal notice requirements.
2. Policies outline coverage determinations for U of U Health Plans Commercial and Healthy U (Medicaid) plans. Refer to the "Policy" section for more information.
3. Services requiring prior-authorization may not be covered, if prior-authorization is not obtained.
4. **This Medical Policy does not guarantee coverage or payment of the service. The service must be a benefit in the member's plan and the member must be eligible for coverage at the time of service. Additional payment guidelines may be applied that are not included in this policy.**

### Description:

Keratoconus is a progressive bilateral eye dystrophy characterized by paracentral steepening and stromal thinning (progressive ectasia) of the cornea that impairs visual acuity. Initial treatment usually consists of hard contact lenses which flatten the corneal and help it maintain its shape. A penetrating keratoplasty (i.e., corneal graft) is the next line of treatment for those individuals who develop intolerance to contact lenses. While visual acuity is typically improved with a keratoplasty, there is an associated risk of perioperative complications, long-term topical steroid use is required and endothelial cell loss occurs over time, which is a particular concern in younger individuals.

As an alternative, a variety of keratorefractive procedures have been attempted. Subtractive techniques include LASIK, but in general, results of this technique have been poor. Next is the implantation of intrastromal corneal ring segments which are intended to reinforce the cornea and prevent further deterioration. The last technique would be a corneal transplantation followed by a corneal graft (penetrating keratoplasty). About 20% of patients with keratoconus will need a corneal transplant. All of these techniques are intended to improve refractive errors, however none of them modify the disease.

Corneal ectasia is a non-inflammatory condition where progressive corneal steepening and thinning occur, whether it is natural (Genetic, mechanical, chromosomal and enzyme abnormalities) or surgically induced (LASIK and PRK). There are different types of corneal ectasia these include pellucid marginal degeneration, keratoglobus, keratoconus, post-

keratorefractive ectasia, and wound ectasia after penetrating keratoplasty (PK). Corneal ectasias can result in significant ocular morbidity and may require surgical intervention.

Corneal collagen cross-linking (CXL) is performed with the photosensitizer riboflavin (vitamin B2) and ultraviolet A (UV-A) irradiation. A common CXL protocol removes about 8 mm of the central corneal epithelium under topical anesthesia to allow better diffusion of the photosensitizer riboflavin into the stroma. Following de-epithelialization, a solution with riboflavin is applied to the cornea (every 1-3 minutes for 30 minutes) until the stroma is completely penetrated. The cornea is then irradiated for 30 minutes with 370 nm ultraviolet A, a maximal wavelength for absorption by riboflavin, while the riboflavin continues to be applied. The interaction of riboflavin and UV-A causes the formation of reactive oxygen species, leading to additional covalent bonds (cross-linking) between collagen molecules, resulting in stiffening of the cornea. Theoretically, by using a homogeneous light source and absorption by riboflavin, the structures beyond a 400-micron thick stroma (endothelium, anterior chamber, iris, lens, and retina) are not exposed to a UV dose that is above the cytotoxic threshold.

## **Policy Statement and Criteria**

### **1. Commercial Plans**

**U of U Health Plans covers epithelium-off corneal cross-linking once per lifetime, per eye if the following criteria are met:**

- A. Patient has a diagnosis of keratoconus or corneal ectasia;
- B. The medicine used is Photrexa Viscous/Photrexa with the KXL devise;
- C. Patient is between the ages of 14 and 65.

**U of U Health Plans does NOT cover corneal cross-linking in conjunction with intrastromal ring segment placement or PRK or phakic intra-ocular lens implantation (CXL-plus) as it is considered investigational.**

**U of U Health Plans does NOT cover epithelium-on (transepithelial) corneal cross-linking for any diagnosis as this is considered investigational.**

### **2. Medicaid Plans**

**Coverage is determined by the State of Utah Medicaid program; if Utah State Medicaid has no published coverage position and InterQual criteria are not available, the U of U Health Plans Commercial criteria will apply. For the most up-to-date Medicaid policies and coverage, please visit their website at: <https://medicaid.utah.gov/utah-medicaid-official-publications/> or the [Utah Medicaid code Look-Up tool](#)**

## **CPT/HCPCS codes covered by Utah State Medicaid may still require further evaluation to determine medical necessity for coverage.**

### **Rationale**

In April 2016, the pharmaceutical and medical device company Avedro received FDA approval for the company's KXL<sup>®</sup> Cross-linking System that provides corneal collagen cross-linking for the treatment of progressive keratoconus. The approval includes Avedro's Photrexa Viscous and Photrexa, which are riboflavin solutions used with the KXL System during the procedure.

The evidence for corneal cross-linking (CXL) in individuals who have keratoconus includes randomized controlled trials (RCTs) and systematic reviews. Relevant outcomes are change in disease status, functional outcomes, and treatment-related morbidity. There is evidence from RCTs, including several pivotal trials, which CXL leads to short-term improvements in corneal steepening, visual acuity compared with untreated eyes, and results from 1 trial have reported that these benefits are maintained at 2 to 3 years. From these RCTs, one can conclude that CXL reduces, and in some cases, reverses the corneal steepening that leads to a reduction in visual acuity in the short term. Greater uncertainty exists regarding the long-term outcomes of CXL for the treatment of keratoconus. Some retrospective studies have reported positive outcomes to 10 years, although these reports have small sample sizes at long-term follow-up and limited information on the entire population of patients treated with CXL during the same time period. There is a need for prospective studies with larger numbers of patients who are followed over many years to determine whether CXL improves longer term outcomes. Several trials are ongoing, and their results are expected soon. Longer term outcomes from large cohorts will also be useful to evaluate potential long-term complications of this new treatment approach.

There have been a large volume of studies published on corneal cross-linking as it has been available in Europe and other parts of the world since approximately 2002. The search of the literature identified 72 primary studies and 8 systematic reviews for inclusion in this review. A full list of the abstracts for these reviews is available in Appendix A. Fourteen of the studies were pediatric studies. As CXL is not FDA approved below age 14, these studies were not included in the overall review. The 63 adult studies included for review involved 3190 patients with outcomes assessed from 1 month to 10 years (Rechichi et al., 2013). Several studies had outcomes to 5+ years (Galvis et al., 2016, Parissi et al., 2016, Kim et al., 2016). Most studies had outcomes 12 months or less. There was significant heterogeneity to the studies with many comparing outcomes of “epi-on versus epi-off” and others exploring standard versus accelerated regimens. Most studies focused on impact on keratometry measurements and not necessarily impact on changes in refraction or reduction in corneal transplantation. Refractive changes are not as impressive as the keratometric measurements, and data from well-designed randomized studies are limited.

On the whole the 8 systematic reviews supported the efficacy of corneal cross-linking in slowing the progression of keratoconus. The reviews were for the most part from 2016, though one went as far back as 2013. This suggests the most up to date information was available in deriving their conclusions. The Hayes review from 2016 epitomizes the findings of the other systematic reviews which not only did evidence seem to support corneal crosslinking as effective and safe but noted the quality of the literature is low (despite the volume – most studies are smaller case series and do not have randomization or controls or are retrospective reviews) and only support “use of conventional corneal cross-linking (C-CXL) for the treatment of progressive keratoconus in adolescent and adult patients).

Only Godefrooij et al. from 2016 looked at the economic implication of this therapy as it relates to corneal transplant. This study retrospectively assessed transplant occurrence over 3 years and noted a 25% reduction. Limiting the ability to generalize this finding in the US, is the fact that this is a Dutch study and corneal transplant access may differ in the Netherlands than in the US. Its retrospective design and lack of other validating studies also limit conclusion on its findings.

Two particular questions related to corneal cross-linking evaluated in the literature are epithelium off (epi-off) vs epithelium on (epi-on) therapy and standard vs. accelerated protocols. Notably, the FDA approval is currently for the standard regimen using the epithelium off method. With regard to the epi-off vs epi-on, 10 studies were identified specifically comparing epi-on vs epi-off. These studies suffer from multiple methodological issues including poor study design (many though comparative were retrospective and lack randomization), were of small size or used different techniques to perform the epi-on portion. These studies generally supported epi-on to have equal benefit to epi-off technique though the study by Gatzioufas et al. from 2016 did not show epi-on to have any benefit on progression of keratoconus. This outcome was also noted in the study by Kocak et al from 2014. Razmjoo et al, 2014 noted "total epithelium off technique resulted in better improvement of K-max and Q-value."

With regard to standard vs accelerated protocols, this review identified 11 studies related to use of an accelerated protocols. One study combined an accelerated protocol with corneal ring implants making conclusions regarding effectiveness murky at best. Many of the other studies suffer from methodological issues similar to those seen with the epi-on vs epi off studies. Many were small case series and others lacked a comparative arm. Additionally, though many employed a 10 minute accelerated protocol several studies used a 5 minute protocol. Many of these studies also were of small size. Nonetheless, the studies tended to demonstrate a beneficial effect on keratometry though they lacked endpoints around visual acuity or corneal transplant impact.

Two studies also looked at corneal cross-linking performed in conjunction with intrastromal corneal rings/implants. One study by Ferenczy et al in 2015 only looked at 31 patients of which only 10 got CXL with as the study by Gordillo et al from 2016 looked at 82 patients. These studies focused on impact on keratometry and corneal shape with relatively short study intervals of 1-2 years. Current evidence is insufficient to draw conclusions as to whether the combination of intrastromal corneal rings and CXL were more effective and safe than either alone.

Lastly, several studies focused on the safety of the procedure. These studies tended to note a slight increase in corneal hazing which occurred more commonly with the epi-off treatment but resolved in approximately 3 months. Overall, this therapy has few short term and no apparent long term safety concerns.

While the goal of therapy is to either halt or reverse a progressive condition (keratoconus or ectasia) the various studies have not all clearly defined "progression". In fact, many studies have either failed to define this starting point of enrollment (eyes with "progressive" disease) or have defined it in a way that may not be acceptable to the ophthalmology community.

In a 2017 randomized, multicenter, controlled trial (Hersh et al) compared patients outcomes with progressive keratoconus over a 1 year time period in 2 ways; First, the change of topography-derived maximum keratometry value; Second, corrected distance visual acuity (CDVA), uncorrected distance visual acuity (UDVA), manifest refraction spherical equivalent, endothelial cell count, and adverse events. In the CXL treatment group, the maximum keratometry value decreased by 1.6 diopters (D) from baseline to 1 year, whereas keratoconus continued to progress in the control group. In the treatment group, the maximum keratometry value decreased by 2.0 D or more in 28 eyes (31.5%) and increased by 2.0 D or more in 5 eyes (5.6%). The CDVA improved by an average of 5.7 logarithm of the minimum

angle of resolution (logMAR) units. Twenty-three eyes (27.7%) gained and 5 eyes lost (6.0%) 10 logMAR or more. The UDVA improved 4.4 logMAR. Corneal haze was the most frequently reported CXL-related adverse finding. There were no significant changes in endothelial cell count 1 year after treatment. It was concluded that corneal collagen cross-linking was effective in improving the maximum keratometry value, CDVA, and UCVA in eyes with progressive keratoconus 1 year after treatment, with an excellent safety profile.

A 2017 updated review (Galvis et al) on patient selection for corneal cross-linking addresses the pediatric population with keratoconus. According to a panel of experts and many authors, if the risk factors suggest progression is more likely CXL is indicated without an age limit. However, there are insufficient randomized control trials for pediatrics, so the majority of the information is theorized from clinical trials and case series in adults. If children have mild disease with good vision, close observation with frequent exams is indicated. If the child presents with a topographically evident keratoconus in a relatively advanced stage, CXL is indicated without waiting to see if there is progression. Most corneal specialists do a case-by-case assessment to determine the risks and benefits before performing the surgery.

A recent review studied 115 out of 210 relevant publications (Perez-Straziota et al, 2018). The review found that treatment with CXL halts progression of keratoconus in the pediatric population, and early treatment seems to be cost-effective compared with later penetrating keratoplasty. However, long-term effects and regression rates remain unclear, and further studies are needed.

A 2018 study (Uysal et al) followed up 1 year later after having corneal cross-linking treatment on 111 eyes of patients diagnosed with keratoconus. At 12 months the following findings had significantly improved; the mean uncorrected visual acuity ( $P < 0.001$ ), best corrected visual acuity ( $P < 0.001$ ), spherical equivalent refraction ( $P < 0.007$ ) and manifest astigmatism refraction ( $P < 0.001$ ). Also corneal topographic measurements were decreased in the mean maximum keratometry, simulated keratometry-1 and keratometry-2 compared with baseline measurements ( $P < 0.001$  for all). The mean root mean square error values for corneal total higher order aberrations ( $P < 0.001$ ), vertical coma ( $P < 0.001$ ) and vertical trefoil ( $P = 0.008$ ). However, the mean modulation transfer function and the Strehl ratio did not change ( $P > 0.05$ ). In conclusion corneal cross-linking led to an improvement in visual, refractive, topographic, and most corneal higher order aberrations outcomes. Unfortunately, the improvements were not enough to increase corneal modulation transfer function and the Strehl ratio of point spread function.

In 2019, Hayes found a very small body of peer-reviewed, published evidence pertaining to the use of concurrent CXL and Intacs/intrastromal corneal ring implantation for the treatment of keratoconus. They found 9 abstracts for this report, 6 of which provided data regarding patient outcomes. Of these 6 studies, only 3 addressed concurrent use of CXL and Intacs and due to the limited amount of available published data, the remaining studies were included for informational purposes only which described outcomes for sequential use of these procedures. Hayes concluded that there is insufficient published evidence to evaluate the safety and /or impact on health outcomes or patient management for these technologies. Larger, further efficient studies are needed to evaluate the concurrent use of these technologies.

In conclusion, the observational evidence for the role of corneal cross-linking has been strong. This data is also supported by several well designed randomized controlled clinical trials. The most consistent finding of observational and randomized controlled studies has been that CXL induces a slight decrease in keratometry values that tends to be maintained over at least a year. This is an important finding, as in progressive keratoconus keratometry typically rises over time and is a marker of disease progression.

## Applicable Coding

### CPT Codes

- 0402T** Collagen cross-linking of cornea (including removal of the corneal epithelium and intraoperative pachymetry when performed)
- 65785** Implantation of intrastromal corneal ring segments

### HCPCS Codes

- J2787** Riboflavin 5'-phosphate, ophthalmic solution, up to 3 mL
- J3490** Unclassified drugs (Photrex)

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